



Till, A., Selwood, J., & Silva, E. (2019). The assertive approach to clozapine: Nasogastric administration. *BJPsych Bulletin*, 43(1), 21-26. <https://doi.org/10.1192/bjb.2018.61>

Publisher's PDF, also known as Version of record

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1192/bjb.2018.61](https://doi.org/10.1192/bjb.2018.61)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via Cambridge University Press at <https://www.cambridge.org/core/journals/bjpsych-bulletin/article/assertive-approach-to-clozapine-nasogastric-administration/D74F1843830F1A58AF6FC852A8D95525#> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

The assertive approach to clozapine: nasogastric administration

Alex Till,¹ James Selwood,² Edward Silva³

BJPsych Bulletin (2019) 43, 21–26, doi:10.1192/bjb.2018.61

¹Psychiatric Trainee, School of Psychiatry, Health Education North West (Mersey), UK; ²Clinical Research Fellow, School of Clinical Sciences, University of Bristol, UK; ³Consultant Forensic Psychiatrist, Ashworth Hospital, Mersey Care NHS Foundation Trust, UK

Correspondence to Dr Edward Silva (ed.silva@merseycare.nhs.uk)

First received 06 Feb 2018, final revision 15 Jul 2018, accepted 24 Jul 2018

© The Authors 2018. This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is unaltered and is properly cited. The written permission of Cambridge University Press must be obtained for commercial re-use or in order to create a derivative work.

Aims and method An ‘assertive approach’ to clozapine, where nasogastric administration is approved, is assessed through a case-load analysis to provide the first systematic description of its use and outcomes worldwide.

Results Five of the most extremely ill patients with treatment-resistant schizophrenia were established and/or maintained on clozapine, resulting in improvements to their mental state; incidents were reduced, segregation was terminated and progression to less restrictive environments was achieved.

Clinical implications Despite being underutilised and rarely enforced, in extreme circumstances, an assertive approach to clozapine can be justified. Nasogastric clozapine can be safely delivered and the approach itself, rather than actual nasogastric administration, may be enough to help establish and maintain patients with treatment-resistant schizophrenia on the most effective treatment.

Declaration of interest E.S. has received speaker fees from Jansen Pharmaceuticals and Novartis.

Keywords Psychotic disorders; psychosis; schizophrenia; antipsychotics; clozapine; nasogastric administration.

The efficacy of clozapine in treatment-resistant schizophrenia is well established.¹ Compared with alternative antipsychotics, clozapine provides superior symptom control, longer duration of treatment, shorter lengths of stay and reduces violence.² Although enforced antipsychotic treatment is generally widespread, clozapine is both underutilised³ and rarely enforced, with only a handful of case reports worldwide reporting the use of nasogastric^{4–6} and intramuscular^{7–9} clozapine.

With injectable clozapine unavailable in the UK until very recently, when presented with a crisis,¹⁰ nasogastric clozapine was successfully used for the first time at Ashworth high-security hospital in 2010 and has been used subsequently to help establish and maintain treatment with clozapine. We now present the first systematic description of the ‘assertive approach’ to clozapine via nasogastric clozapine, which commences not on the first administration of nasogastric clozapine, but on its approval for use; this in itself is often enough.

Methods

A retrospective case-load analysis of E.S.’s patients was conducted on an intent-to-treat basis, defined by the presence of a Second Opinion Appointed Doctor (SOAD) request for the authorisation of nasogastric clozapine, from the first case in

2010 through to 2016. This provided a minimum 12-month follow-up period. Clinical records were reviewed to identify patient demographics and clinical details including medication compliance and response to treatment, which was determined by Clinical Global Impression (CGI) scores¹¹ combined with segregation use and incident frequency for 12 months before and after SOAD approval for nasogastric clozapine.

The method used to deliver nasogastric clozapine is outlined within [Box 1](#).

Results

E.S. had cared for five patients, whose demographics can be seen in [Table 1](#), where a SOAD approved the administration of clozapine via a nasogastric tube. All were diagnosed with treatment-resistant schizophrenia (ICD-10 code F20¹²), all were confined in their rooms because of risk to others (long-term segregation¹³) and all were considered to be among the most extremely ill patients encountered within this particular population (CGI score of 7 for severity of illness).

For all patients, their families, advocates and/or legal team were consulted. None objected.

At the time the assertive approach to clozapine was initiated (i.e. SOAD approval for its use was gained), two patients had not started clozapine and three patients had

Box 1. How to deliver nasogastric clozapine.*Clozapine preparation*

Although several brands of clozapine are available and unlicensed ‘special’ oral suspensions can be prepared (including crushed tablets), we advocate the use of Denzapine as this is currently the only licensed oral suspension in the UK. If an alternate clozapine provider is currently in operation, then registration of the hospital and prescribing psychiatrist with a second supplier are necessary before transferring the patient’s registration. This risks using two clozapine monitoring systems in one hospital, with possible confusion regarding dispensing medication and liaising with different clozapine-monitoring services as well as the potential of having to switch providers once the patient is established on tablet medication.

Restraint

A thorough risk assessment is required to ensure adequate numbers of trained, competent and resilient staff are present and it is essential they are well supported by the leadership team; consultant presence was initially provided, being replaced by more junior medical staff when confidence grew. At least one member of Resus Council (UK) ‘Immediate Life Support’ trained member of staff must be present. Throughout every intervention, patients should be repeatedly given the option of taking oral clozapine. Mechanical restraint was considered as an option but, even with our most difficult patients, was neither planned nor used. Manual restraint was sufficient with between two and six members of staff; in the most extreme cases one member of staff was allocated to each limb, with two controlling the head. Patients were usually seated upright on the edge of their bed, with their neck in line with their back. Precautions may be required to mitigate risks of spitting and biting, including lightweight disposable face visors and gloves.

Nasogastric tube placement

Appropriate training for both medical and nursing staff can be arranged with a general hospital clinical skills team. Fine bore feeding tubes should be used. The first-line, gold-standard method of confirming placement in the stomach is by demonstrating a gastric pH of ≤ 5.5 .¹⁴ Acid-inhibiting medication reduces the sensitivity but does not alter the specificity or render the method unsafe¹⁴; actions to reduce this risk should be considered. Radiological confirmation is not required.¹⁴ Once placement is confirmed, nursing staff can administer the clozapine, which varies in volume (50 mg/ml) throughout titration. Unless safe to leave *in situ*, the nasogastric tube should be removed immediately after clozapine administration.

Legal authority

In England and Wales, incapacitous or non-consenting patients detained under the Mental Health Act 1983 may be administered drug treatments for mental disorders for longer than 3 months only if a Second Opinion Appointed Doctor (SOAD) approves the treatment, including the route of administration. Personal communication from the principal SOAD has indicated that the oral and nasogastric routes are equivalent: both are enteral.

Ethical dilemmas

Explored by Silva *et al*¹⁰, there are ethical dilemmas with administering nasogastric clozapine. These involve balancing the risks and benefits of an unacceptable status quo against the uncertainties of the possible risks and benefits of intervention, alongside containing and resolving the emotions of the team when using a novel, restrictive and coercive treatment on a vulnerable and incapacitous patient.

started clozapine but were not reliably compliant (median duration of 31 days); ultimately, only three patients received nasogastric clozapine and other than the use of restraint, no adverse incidents occurred.

Patient 1 commenced clozapine after SOAD approval and received four doses of nasogastric clozapine on non-consecutive occasions over a period of 3 weeks, before being

established on oral clozapine. Patient 2 only commenced oral clozapine after SOAD approval for nasogastric clozapine, but nasogastric administration itself was never required. Patient 3 commenced oral clozapine after persuasion, but threatened to stop and SOAD approval was enough to maintain compliance without nasogastric administration being necessary. Patient 4 took oral clozapine for 1 month

Table 1 Patient demographics

Patient	Age at first episode of psychosis	Age at admission to high-security services	Age at SOAD approval of nasogastric clozapine	Duration of illness at SOAD approval of nasogastric clozapine	Length of stay in high-security services at SOAD approval of nasogastric clozapine	Primary diagnosis	Admission source	Mental Health Act section on admission
1	19	43	43	24	98 days	F20.3	Medium-security hospital	3
2	21	27	43	22	16 years	F20.0	Prison	47/49
3	21	33	35	14	2 years	F20.0	Prison	47/49
4	19	39	45	26	5 years	F20.0	Medium-security hospital	37/41
5	15	25	33	18	8 years	F20.3	Medium-security hospital	3

Age and duration of illness is presented in years. Primary diagnosis is given by ICD-10 code (see ICD-10 for full definitions). SOAD, Second Opinion Appointed Doctor.

but then repeatedly threatened to refuse. SOAD approval was sought and nasogastric clozapine was administered once, which was enough to maintain compliance thereafter. Patient 5 maintained erratic compliance with oral clozapine and despite taking it for 617 days, was approved for nasogastric clozapine because of life-threatening clozapine withdrawal catatonia that had previously been unresponsive to benzodiazepines or electroconvulsive therapy (ECT). In the 12 months after SOAD approval for nasogastric clozapine, he received it four times on non-consecutive occasions over the first 6 months.

All five patients were considered to have shown a global improvement on CGI scores after the initiation of an assertive approach to clozapine, with the drug efficacy index showing that, for the majority of patients, clozapine had resulted in a 'vast' or 'decided' improvement in their condition (Table 2). Across all five patients, incidents reduced from an average of 72 over the 12 months before SOAD approval to 29 in the 12 months after SOAD approval. No patients were unchanged or worse, and only patient 5 remained in segregation beyond 12 months (terminated on the 476th day). Therefore, despite a significant reduction in incidents (Fig. 1), they were registered as having only minimally improved according to their CGI score.

Our most recent data (with a minimum follow-up of 2 years after SOAD approval for nasogastric clozapine) demonstrates that none of the five patients required clozapine re-titration, and that all are now compliant with clozapine (although patient 5 did require a nasogastric tube to be passed on one occasion before accepting clozapine orally nearly 2 years (626 days) after it was last administered nasogastrically).

Discussion

The majority of patients are transferred to high-security hospitals in the UK because the severity of their psychotic-driven violence is considered to be uncontrollable elsewhere, and a large proportion of the patient population already complies with clozapine without using what we can only describe as a highly assertive approach.¹⁵ This is reserved for those with the most severe and debilitating conditions. They have often been detained for decades, with some spending years in segregation despite persistent attempts at engagement in psychological work and/or numerous trials of both evidence-based and/or other none or weakly evidence-based treatments (including failed attempts on clozapine secondary to poor compliance), commonly including treatment with high-dose and/or multiple antipsychotics, which are both unlikely to work and hazardous to the individual.^{16,17}

Although all health professionals prefer to initiate treatments with patients who fully understand and actively consent and cooperate, in these rare cases, the status quo is clearly unacceptable and the ethical argument for this very assertive approach to clozapine, once conceived of, is not hard to make to establish and maintain patients on clozapine.¹⁰

However, a survey of psychiatrists working in psychiatric intensive care units in the UK found that even restraint to take bloods for clozapine was very rarely reported and

Table 2 Patient outcomes, including Clinical Global Impression scores, time in segregation and referral/transfer status

Patient	Clinical Global Impression scores (>12 months post-SOAD)	Severity of illness	Global improvement	Efficacy index	Days in segregation (total pre-SOAD)	Days in segregation (12 months pre-SOAD)	Days in segregation (12 months post-SOAD)	Transfer out of high-security dependency unit	Referral out of high-security services	Transfer out of high-security services
1	7	2	2	06	98	98	133	No	Yes	Yes
2	7	1	1	02	1046	280	94	Yes	Yes	Yes
3	7	2	2	06	37	37	98 ^a	Yes	No	No
4	7	2	2	06	2094	365	287	No	Yes	Yes
5	7	3	3	09	2492	365	365	No	Yes	No

a. Fourteen additional episodes of seclusion totalling 80 days.

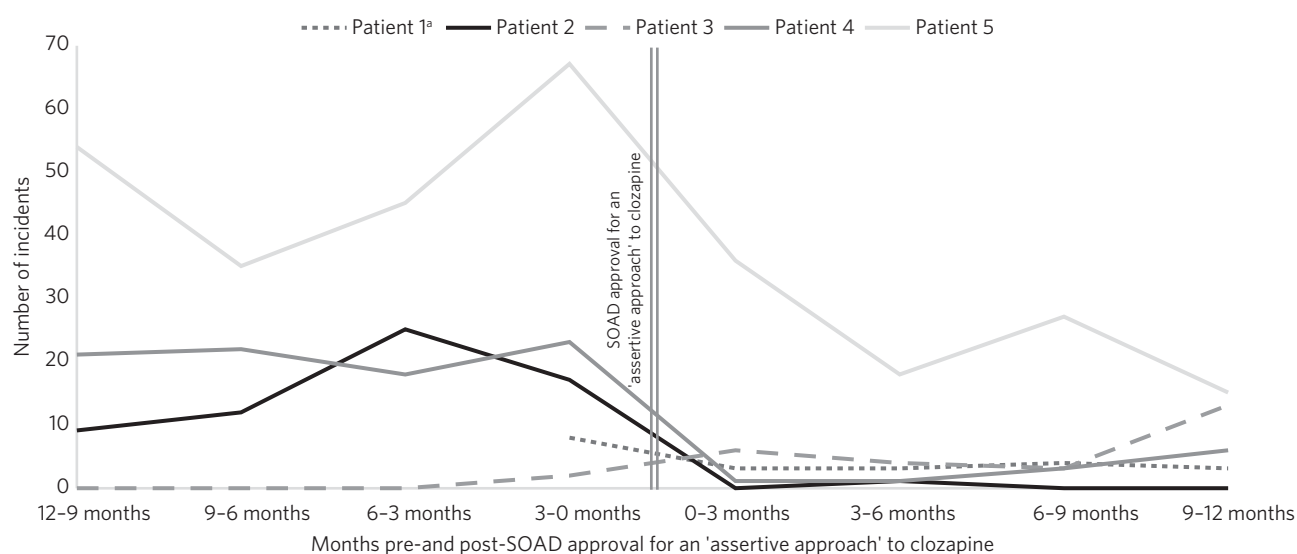


Fig. 1 Incident frequency in the 12 months pre- and post-SOAD approval for an assertive approach to clozapine. SOAD, Second Opinion Appointed Doctor. a. Incident data for patient 1 was unavailable beyond 3 months before SOAD approval as they had not been admitted.

attitudes towards it were variable, with a significant minority describing it as never appropriate.¹⁸ The same author's description of an approach to enforcing clozapine, including taking bloods in restraint,¹⁹ resulted in critical responses: one expressing dismay that the article was published at all,²⁰ and the other setting out why it would not work.²¹

Our results demonstrate that simply accepting refusal of clozapine from a patient with treatment-resistant schizophrenia can deprive them of the benefits that this significantly superior (compared with all other antipsychotics²²) and recommended treatment of choice provides, and how an assertive approach to clozapine, rather than actual nasogastric administration, can help initiate and maintain treatment leading to improvements in mental state, reductions in incidents, terminations of seclusion and transfers to less restrictive environments.

These results were not unexpected, given the unique properties of clozapine on treatment-resistant schizophrenia and violence.² Neither was the sometimes significant period of decompression before segregation was stopped, as despite some patients having a rapid improvement and almost immediate cessation of incidents of aggression or violence, they had significant histories of being involved in dramatic and disabling assaults against staff and therefore extreme caution was exercised.

What was clinically unexpected, given the individual patient histories, was the surprising level of cooperation. There were fewer restraints and enforced nasogastric clozapine administrations than had been expected, and one patient who had repeatedly refused oral clozapine for years cooperated without nasogastric administration at all, although this was also a finding when intramuscular clozapine was enforced in the Netherlands.²³

It is possible that teams redoubled their efforts, that patients were aware of the possibility of restraint and were coerced by the prospect alone or that patients regained a level of insight, or even a combination of the three; it is difficult to tell.

As Silva *et al*¹⁰ discuss, teams that embark on this approach are faced with very difficult decision-making, such as how long to persist with one attempt at passing a nasogastric tube? When is a patient's distress at the procedure too great? And how many times should clozapine be administered via a nasogastric tube before accepting that oral compliance will not be maintained? These questions are not easy to answer, and the judgements can only be made by individual teams and will vary on their own capacity to maintain treatment and a relationship with a patient in very difficult circumstances.

For some patients their previous refusals will be based on psychotic motivations and it is hoped that these patients may quite rapidly respond. Others may have a combination of psychotic, personal and possibly comorbid motivations that may not be remedied by either clozapine or this assertive approach. For these patients, we would not advocate the regular use of nasogastric administration of clozapine as a long-term solution. We know, particularly when huge effort and resources are expended on initiatives, that there can be a tendency to get stuck in a persisting course of action or to fail to consider alternative approaches²⁴ (although in this case many of these are less likely to work²⁵), and teams must be careful not to fall into this trap.

One good alternative, with local guidelines emerging,²⁵ is the option of trying to establish patients on clozapine by an assertive approach with intramuscular injections. Having recently become available again, intramuscular clozapine may be preferred to nasogastric clozapine, given the less intrusive and unpleasant method of administration. However, unlike nasogastric clozapine, intramuscular clozapine is limited by the deliverable dose and therefore duration of treatment, with large volumes required (25 mg/ml) as the titration increases toward the average UK dosage of around 450 mg/day.²⁶ Intramuscular clozapine also remains an unlicensed product, with an increased likelihood of prone restraint and a theoretical risk of accidental intravenous administration. Therefore, although intramuscular

clozapine provides an additional treatment option, nasogastric clozapine can continue to have an important role to prevent re-titration and administer clozapine when the maximum deliverable dose of intramuscular clozapine is insufficient.

Another alternative, where an assertive approach to clozapine fails or for the significant number of patients who do not respond to clozapine monotherapy or clozapine augmentation strategies, is the more restrictive treatment of ECT, which may well be the most appropriate next step.²⁷ However, for the cohort we describe, this intervention is particularly difficult to deliver and maintain the safety of both staff and patients.

Ethically, what remains is a real argument about the wrongs of a failure to treat the most severely ill patients with treatment-resistant schizophrenia against the perceived wrongs of nasogastric clozapine. Clearly, this approach can never be a panacea; clozapine can often not be used (because of adverse effects) and nearly 50% of patients fail to achieve a satisfactory therapeutic response.²⁸ However, for those who have suffered with the most debilitating conditions imaginable, clozapine can result in dramatic and seemingly unexpected improvements in mental state and function. Accepting a patient's refusal of treatment and failing to offer them that chance of improvement via an assertive approach to clozapine through nasogastric administration seems, in our opinion, cruel and unnecessary.

Conclusion

Our case series shows that nasogastric clozapine can be safely delivered and that the approach itself, rather than actual nasogastric administration, may be enough to establish and maintain treatment with clozapine.

An assertive approach to clozapine can therefore play an important role in managing patients with treatment-resistant schizophrenia. It can be justified to help reduce patients' extreme suffering and distress as a result of their psychosis, can be expanded in a variety of psychiatric in-patient settings and can help reduce the usually disappointing outcomes seen with other drugs or drug combinations.

This is the first systematic description of the assertive approach to clozapine and helps counter likely objections regarding the efficacy and risk of administering nasogastric clozapine that might otherwise prevent or delay patients with treatment-resistant schizophrenia receiving the recommended treatment of choice.

About the authors

Alex Till is a psychiatric trainee in the School of Psychiatry at Health Education North West (Mersey), UK. **James Selwood** is a clinical research Fellow in the School of Clinical Sciences at the University of Bristol, UK. **Edward Silva** is a consultant forensic psychiatrist at Ashworth Hospital, Mersey Care NHS Foundation Trust, UK.

References

- Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2016; **209**(5): 385–92.
- Frogley C, Taylor D, Dickens G, Picchioni M. A systematic review of the evidence of clozapine's anti-aggressive effects. *Int J Neuropsychopharmacol* 2012; **15**(9): 1351–71.
- Mistry H, Osborn D. Underuse of clozapine in treatment-resistant schizophrenia. *Adv Psychiatric Treat* 2011; **17**(4): 250–5.
- Fisher WA. Elements of successful restraint and seclusion reduction programs and their application in a large, urban, state psychiatric hospital. *J Psychiatr Pract* 2003; **9**(1): 7–15.
- Mossman D, Lehrer DS. Conventional and atypical antipsychotics and the evolving standard of care. *Psychiatr Serv* 2000; **51**(12): 1528–35.
- Mossman D. Unbuckling the "chemical straightjacket": the legal significance of recent advances in the pharmacological treatment of psychosis. *San Diego Law Review* 2002; **39**: 1033–164.
- Lokshin P, Lerner V, Miodownik C, Dobrusin M, Belmaker RH. Parenteral clozapine: five years of experience. *J Clin Psychopharmacol* 1999; **19**(5): 479–80.
- McLean G, Juckes L. Parenteral clozapine (Clozaril). *Australas Psychiatry* 2001; **9**(4): 371.
- Kasinathan J, Mastroianni T. Evaluating the use of enforced clozapine in an Australian forensic psychiatric setting: two cases. *BMC Psychiatry* 2007; **7**(1): 13.
- Silva E, Till A, Adshead G. Ethical dilemmas in psychiatry: when teams disagree. *BJPsych Adv* 2017; **23**(4): 231–9.
- Guy W. The Clinical Global Impression Scale. In *ECDU Assessment Manual for Psychopharmacology. Revised DHEW Pub. (ADM):* 218–22. National Institute for Mental Health, 1976.
- World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization, 1996.
- Department of Health. *Mental Health Act 1983: Code of Practice*. London: TSO, 2015.
- National Patient Safety Agency. *Patient Safety Alert NPSA/2011/PSA002: Reducing Harm Caused by Misplaced Nasogastric Feeding Tubes in Adults, Children and Infants*. NHS, 2011.
- Swinton M, McNamee H. Clozapine in forensic settings: persuading patients. *Br J Forensic Pract* 2003; **5**(2): 33–8.
- Correll CU, Rubio JM, Inczedy-Farkas G, et al. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry* 2017; **74**(7): 675–84.
- Royal College of Psychiatrists. *CR190 Consensus Statement on High-Dose Antipsychotic Medication*. Royal College of Psychiatrists, 2014.
- Pereira S, Beer D, Paton C. Enforcing treatment with clozapine: survey of views and practice. *Psychiatrist* 1999; **23**(6): 342–5.
- Pereira S, Beer D, Paton C. When all else fails. A locally devised structured decision process for enforcing clozapine therapy. *Psychiatr Bull* 1999; **23**(11): 654–6.
- Fahy TJ. Martial arts for psychiatrists. *Psychiatrist* 2000; **24**(5): 197–8.
- Barnes TRE. Commentary: the risks of enforcing clozapine therapy. *Psychiatrist* 1999; **23**(11): 656–7.
- Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; **382**(9896): 951–62.
- Schulte PF, Stienen JJ, Bogers J, Cohen D, Van Dijk D, Lionarons WH, et al. Compulsory treatment with clozapine: a retrospective long-term cohort study. *Int J Law Psychiatry* 2007; **30**(6): 539–45.
- Staw BM. Knee-deep in the big muddy: a study of escalating commitment to a chosen course of action. *Organ Behav Hum Perform* 1976; **16**(1): 27–44.

- 25 Sussex Partnership NHS Foundation Trust. *Protocol for the Use of Intramuscular (IM) Clozapine Injection*. Sussex Partnership NHS Foundation Trust, 2017 (http://www.sussexpartnership.nhs.uk/sites/default/files/documents/im_cloz_-_trust_protocol_v1_-_0417_-_final.pdf).
- 26 Taylor D, Mace S, Mir S, Kerwin R. A prescription survey of the use of atypical antipsychotics for hospital patients in the UK. *Int J Psychiatry Clin Pract* 2000; **4**: 41-6.
- 27 Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry* 2015; **172**(1): 52-8.
- 28 Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45**(9): 789-96.

